From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

10/PCT/PTO 22 FEB 2005

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20 DEC 2004

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	15.12.2004
Applicant's or agent's file reference: AFB/JAS/P9691WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 03/03692	22.08.2003	26.08.2002

Applicant
S.L.A. PHARMA AG et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference AFB/JAS/P9691WO	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 03/03692	International filing date *(day/month/year)* 22.08.2003	Priority date *(day/month/year)* 26.08.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/4164		
Applicant S.L.A. PHARMA AG et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.03.2004	15.12.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Sindel, U Telephone No. +49 89 2399-7064

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-11	as originally filed

Claims, Numbers

1-27	as originally filed
28-64	received on 05.07.2004 with letter of 01.07.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 48-64

   because:

   ☒ the said international application, or the said claims Nos. 48-64 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☒ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-64
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-64
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-47
	No:	Claims	

2. Citations and explanations

see separate sheet

Reference is made to the documents cited in the search report. They are numbered accordingly.

Item III

Claims 48-64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Item V

1) **Novelty**

The subject matter of claims 1-64 seems to be new in the sense of Article 33(2) PCT in view of the prior art.

2) **Inventive step**

The subject matter of claims 1-64 seems to involve an inventive step in the sense of Article 33(3) PCT in view of the prior art.

The problem to be solved is the provision of a high-concentrated metronidazole formulation for topical treatment of diseases in the colon and rectum.
The solution provided is a medicament comprising at least 5% of metronidazole in a non-aqueous vehicle like white petrolatum.

D1 discloses a formulation comprising 0.8% of metronidazole in water (see page 463, column 1, paragraph 6). The formulation was used for the local treatment of pouchitis which occured on patients after being operated of ulcerative colitis (see page 462, column 2, paragraph 1).
D2 describes a topical composition comprising 1-2% of metronidazole in white petrolatum which is used for the application to the eye (see examples 8-10 and column 1, lines 5-11).
D3 mentions the rectal application of metronidazole for local therapy (see page 8, lines 1-6).
D4 describes the oral use of metronidazole for the treatment of Crohn's disease and associated fistulae (see abstract).

The subject-matter of present claims 1-64 seems to be new and inventive in view of the prior art.

3) **Industrial applicability**

For the assessment of the present claims 48-64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The subject matter of claims 1-47 is industrially applicable in the sense of Article 33(4) PCT.

replaced by Art. 34

28. A topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle for use in the treatment of the human or animal body.

29. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to relieve pain caused by conditions of the colon, rectum, anorectum or perianal region.

30. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a medicament to relieve pain following a surgical operation to the colon, rectum, anorectum or perianal region.

31. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to reduce inflammation following a surgical operation to the colon, rectum, anorectum or perianal region.

32. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to promote healing following a surgical operation to the colon, rectum, anorectum or perianal region.

33. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to reduce edema following a surgical operation to the colon, rectum, anorectum or perianal region.

34. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to reverse tissue induration and granulation following a surgical operation to the colon, rectum, anorectum or perianal region.

Replaced by Art. 34

35. Use as claimed in any of Claims 30 to 34 wherein the surgical operation is an anorectal operation.

36. Use as claimed in Claim 35 wherein the surgical operation is selected from a hemorrhoidectomy, a fistulotomy, a fissurectomy, a sphincterotomy, sphincteroplasty or incision and drainage of an abscess.

37. Use as claimed in Claim 36 wherein the surgical operation is a hemorrhoidectomy.

38. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to treat conditions of the colon, rectum, anorectum or perianal region.

39. Use as claimed in Claim 38 wherein the condition is selected from inflammatory bowel disease, ulcerative colitis, perianal Crohn's disease, radiation proctitis, idiopathic proctocolitis or pouchitis.

40. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to treat anorectal or perianal ulcers or skin defects.

41. Use as claimed in Claim 40 wherein the ulcers are infective or inflammatory ulcers.

42. Use as claimed in Claim 41 wherein the ulcers are HIV- or radiation induced.

43. Use as claimed in Claim 41 wherein the ulcers are erosive ulcers resulting from chronic diarrhea or anorectal incontinence.

44. Use as claimed in Claim 41 wherein the ulcers are associated with inflammatory bowel

Replaced by Art. 34

disease.

45. Use of metronidazole or a pharmacologically acceptable derivative thereof in the manufacture of a topical medicament to treat perianal infective or inflammatory processes.

46. Use as claimed in Claim 45 wherein the process is selected from perianal abscess, fissure in ano, hindradenitis, pilonidal abscess or sinus.

47. Use as claimed in any of Claims 29 to 46 wherein the topical medicament comprises the composition defined in any of Claims 1 to 28.

48. A method of relieving pain caused by conditions of colon, rectum, anorectum and perianal region of the human or animal body comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

49. A method of relieving pain following a surgical operation to the colon, rectum, anorectum and perianal region of the human or animal body comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

50. A method of reducing inflammation following a surgical operation to the colon, rectum, anorectum and perianal region of the human or animal body comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

51. A method of promoting healing following a surgical operation to the colon, rectum, anorectum

replaced by Art 34

and perianal region of the human or animal body comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

52. A method of reducing edema following a surgical operation to the colon, rectum, anorectum and perianal region of the human or animal body comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

53. A method of reversing tissue induration and granulation following a surgical operation to the colon, rectum, anorectum and perianal region of the human or animal body comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

54. A method as claimed in any of Claims 49 to 53 wherein the surgical operation is selected from a hemorrhoidectomy, a fistulotomy, a fissurectomy, a sphincterotomy, sphincteroplasty or incision and drainage of an abscess.

55. A method of treatment of conditions of the colon, rectum, anorectum and perianal region comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

56. A method as claimed in Claim 55 wherein the condition is selected from inflammatory bowel disease, ulcerative colitis, perianal Crohn's disease, radiation proctitis, idiopathic proctocolitis or pouchitis.

Replaced by Art. 34

57. A method of treatment of anorectal or perianal ulcers comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

58. A method of treatment of perianal infective or inflammatory processes comprising application of a topical composition comprising metronidazole or a pharmacologically acceptable derivative thereof at a concentration of at least about 5 wt % in a pharmacologically acceptable non-aqueous vehicle directly to the affected area.

59. A method of treatment of conditions of the colon, rectum, anorectum and perianal region comprising application of a topical composition as defined in any of Claims 1 to 28 to the affected area.

60. A method as claimed in any of Claims 48 to 59 wherein the dose of metronidazole for each application is between from about 125 mg to about 1250 mg.

61. A method as claimed in any of Claims 48 to 60 wherein the dose of metronidazole for each application is between from about 125 mg to about 375 mg.

62. A method as claimed in any of Claims 48 to 61 wherein the dose of metronidazole for each application is about 250 mg.

63. A method as claimed any of Claims 48 to 62 wherein the composition is applied between from 2 to 4 times daily.

64. A method as claimed in any of Claims 48 to 63 wherein the composition is applied 3 times daily.